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GE11 peptide-conjugated nanoliposomes to enhance the combinational therapeutic efficacy of docetaxel and siRNA in laryngeal cancers

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ORIGINAL RESEARCH

GE11 peptide-conjugated nanoliposomes to enhance the combinational therapeutic efficacy of docetaxel and siRNA in laryngeal cancers

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Abstract: In this study, dual therapeutic-loaded GE11 peptide-conjugated liposomes were developed and applied to enhance therapeutic efficacies of standard-of-care regimens for the treatment of laryngeal cancer. The therapeutic strategy used here was a combination treatment with the chemotherapeutic docetaxel (DTX) and siRNA against the ABCG2 gene that regulates multidrug resistance in many tumor types. Liposome-encapsulated DTX/ABCG2–siRNA molecules were targeted to recognize tumor cells of squamous morphology by conjugation to the EGFR-targeting ligand, GE11. Targeted, drug-infused liposomes were nanosized and exhibited controlled release of DTX. Presence of GE11 peptides on liposomal surfaces enhanced the quantities of liposomal constructs taken up by Hep-2 laryngeal cancer cells. GE11 peptide-conjugated liposomes also enhanced cytotoxic effects against Hep-2 laryngeal cancer cells when compared to treatment with free DTX, thereby reducing IC_{50} values. Additionally, GE11 peptide-conjugated liposomes had significantly increased anti-tumor and apoptotic effects. Treatments with the GDSL nanoparticle formulation inhibited tumor growth in Hep-2 xenograft-bearing nude mouse models when compared to treatments with non-targeted NP constructs. Treatment of the mouse models with GE11 peptide-conjugated liposomes mitigated toxicities observed after treatment with free DTX. Taken together, liposomal encapsulation of DTX and ABCG2–siRNA improved the anti-tumor effects of treatment with free DTX in Hep-2 cell lines, and conjugation of GE11 peptides to liposomal constructs enhanced anti-tumor efficacies and specificities in laryngeal cancer cells.

Keywords: laryngeal cancer, docetaxel, ABCG2–siRNA, anti-tumor efficacy, liposomal chemotherapy carriers, GE11 peptide-targeted liposomes

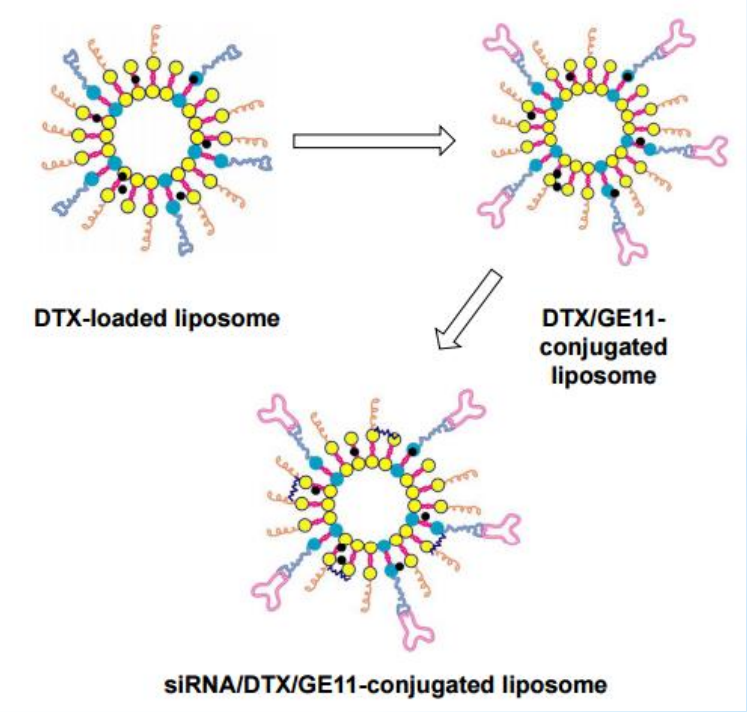
Background

* Mortality and incidence rate in laryngeal cancer.
* Treatment options for laryngeal cancers include surgery, radiotherapy, and chemotherapy.
* In chemotherapy, DTX acts by stabilizing the microtubule apparatus, thereby inhibiting cell division.
* Poor solubility and wide systemic side effects ,and multidrug resistance (MDR) are a barrier of chemotherapeutic agents that reduces therapeutic efficacy.

Background

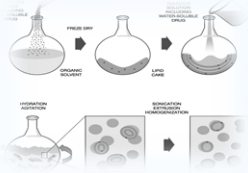
* ABCG2 gene
* The therapeutic strategy was used here was a combination treatment.
* Liposome as carrier
* EGFR and overexpression in laryngeal cancer
* A novel peptide, GE11 (YHWYGYTPQNVI) was specificity against EGFR proteins.

* In this paper, DTX loaded within the hydrophobic lipid bilayer.
* ABCG2–siRNA polynucleotides were loaded on liposomal surfaces using electrostatic interactions.
* Liposomal surfaces were also conjugated with GE11.



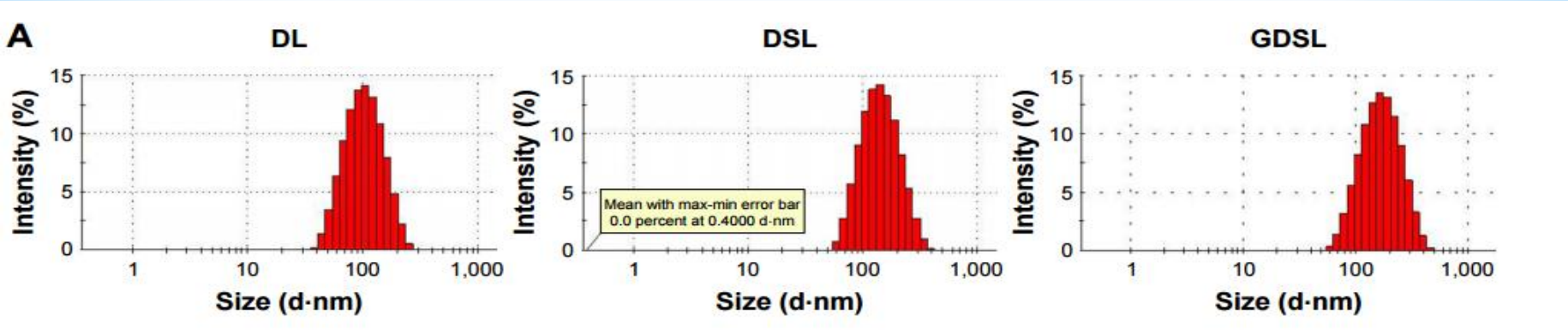
Methods

1. Preparation of drug-loaded liposomes and peptide conjugations.
2. Particle size analyses.
3. Morphology analyses.
4. In vitro drug release assays.
5. In vitro cell viability assays of Hep-2 cells.
6. Apoptosis assays
7. Hoechst 33382 staining assays
8. In vivo anti-tumor efficacy studies
9. Statistical analyses



Results and discussion

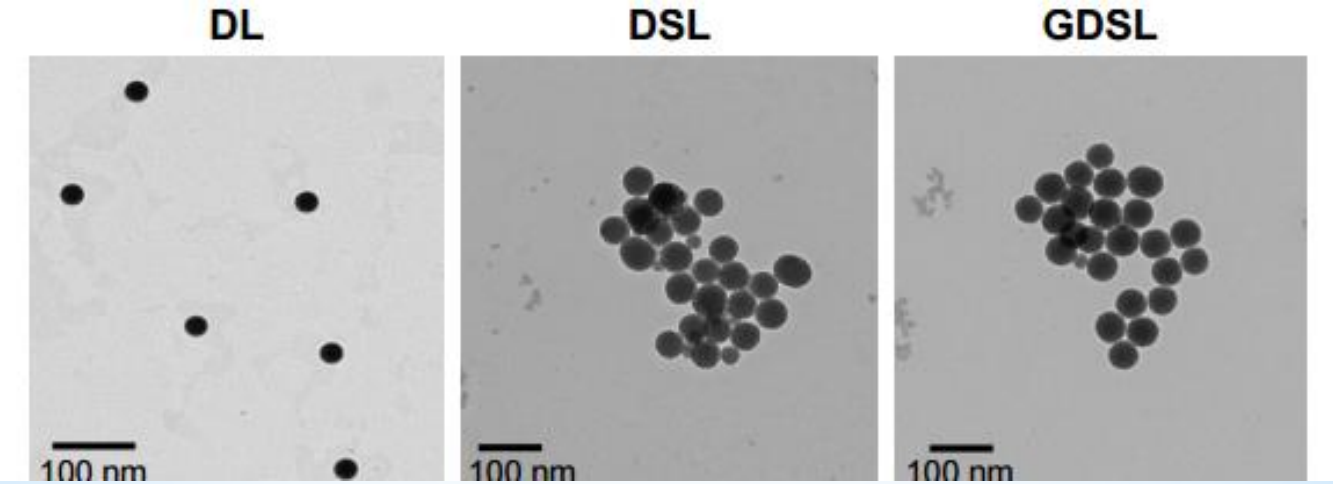
1. **Physicochemical analyses of GE11 peptide-conjugated DTX/ABCG2–siRNA-loaded liposomes.**



- The mean diameters of DTX/liposomes were ~110 nm
- Conjugations of GE11 peptides increased NP sizes to approximately 150 nm
- Final DTX/ABCG2–siRNA-loaded NPs were of mean size ~180 nm.

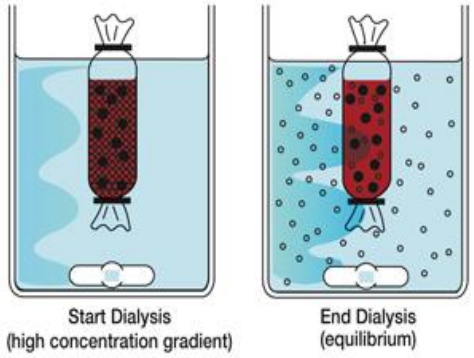
Results and discussion

GE11-conjugated DTX/ABCG2–siRNA loaded liposomes were slightly larger than DTX/liposomes and maintained spherical morphologies, indicating that **surface modifications did not alter the shapes of the NPs.**



Results and discussion

2- Drug-release studies



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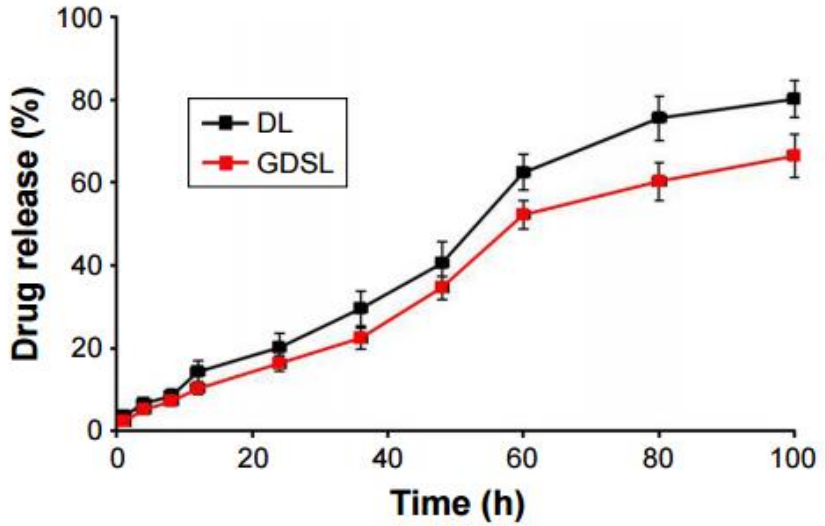
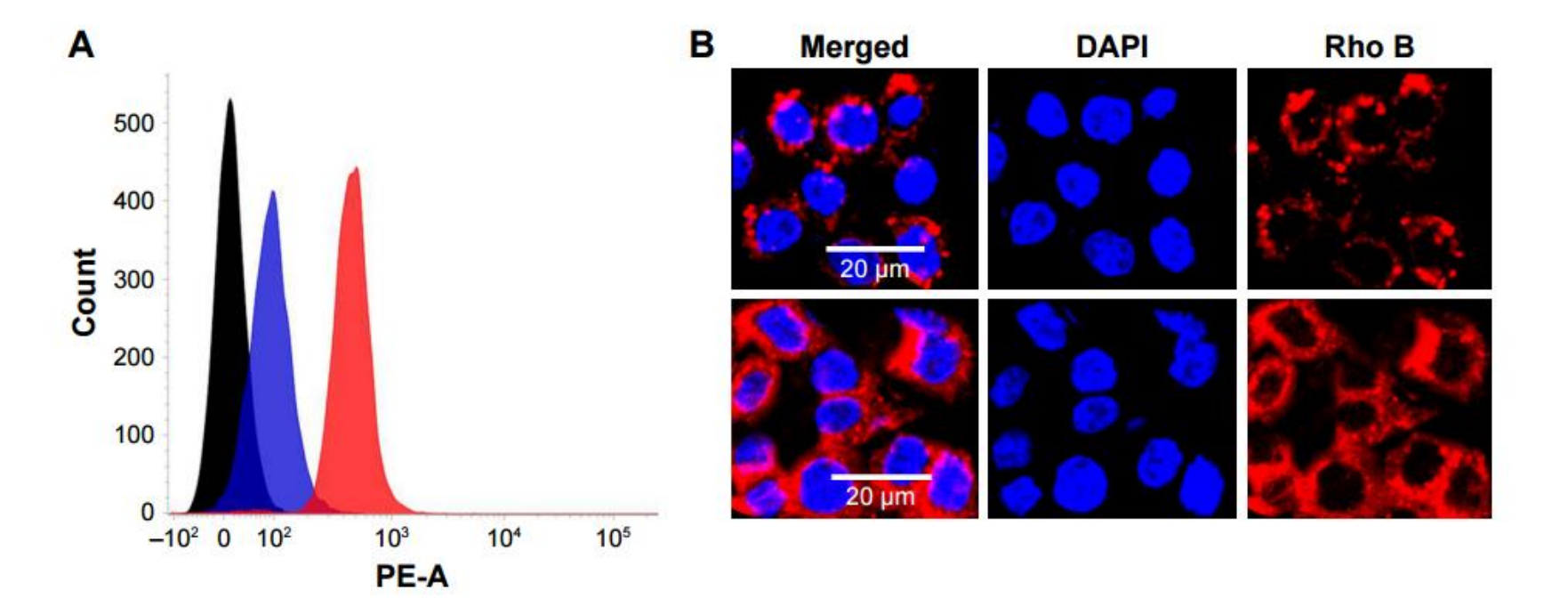


Figure 3 In vitro drug release assays measuring loss of DTX from DL and GDSL constructs.
Note: The release study was performed using dialysis methods at 37°C.
Abbreviations: DL, DTX-loaded liposome; DTX, docetaxel.

- the in vitro drug release assays were determined by dialysis methods in PBS (pH 7.4) at 37°C

Results and discussion

3- Cellular uptake analyses



- Rhodamine-B fluorescence intensities were observed in cytoplasmic regions, suggesting that NPs were internalized via endocytosis-mediated mechanisms.

Results and discussion

4- In vitro cytotoxic effects of GE11-targeted DTX/ABCG2-liposomal NPs

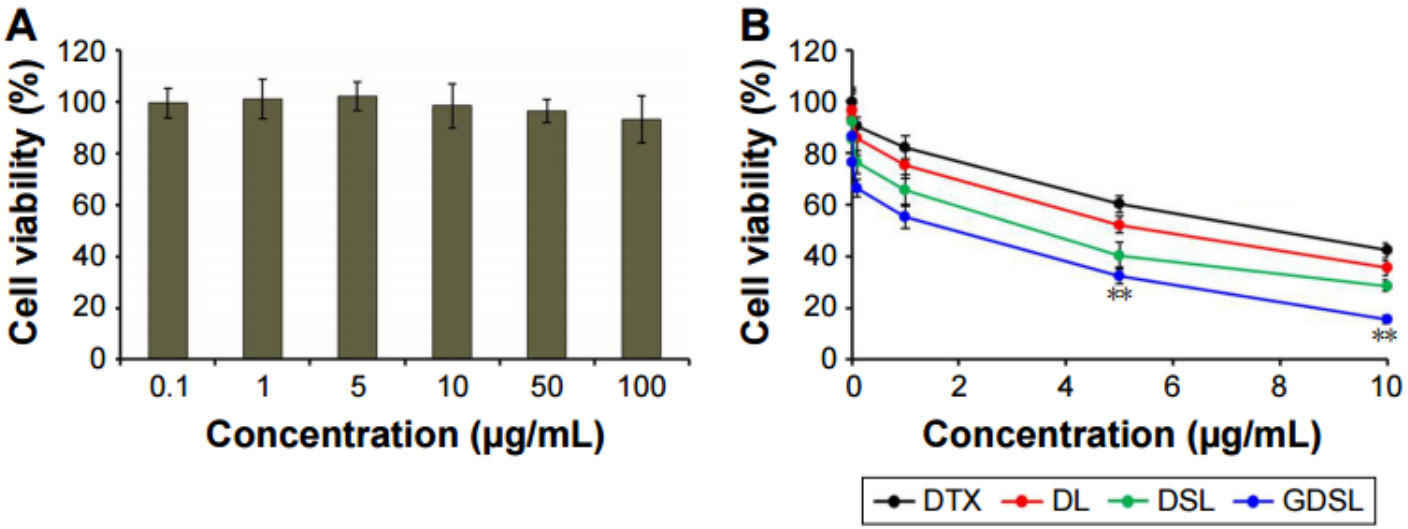


Figure 5 In vitro cytotoxic analyses of (**A**) empty NPs and (**B**) DTX/ABCG2–siRNA-loaded NPs.
Notes: The cells were treated with a concentration gradient of each NP formulation and then evaluated by MTT assays. $^{**}P<0.001$ is the statistical difference between DL and GDSL.
Abbreviations: DL, DTX-loaded liposome; DTX, docetaxel; DSL, DTX and siRNA-loaded liposome; DTX, docetaxel; NP, nanoparticle.

Results and discussion

5- Apoptosis assays

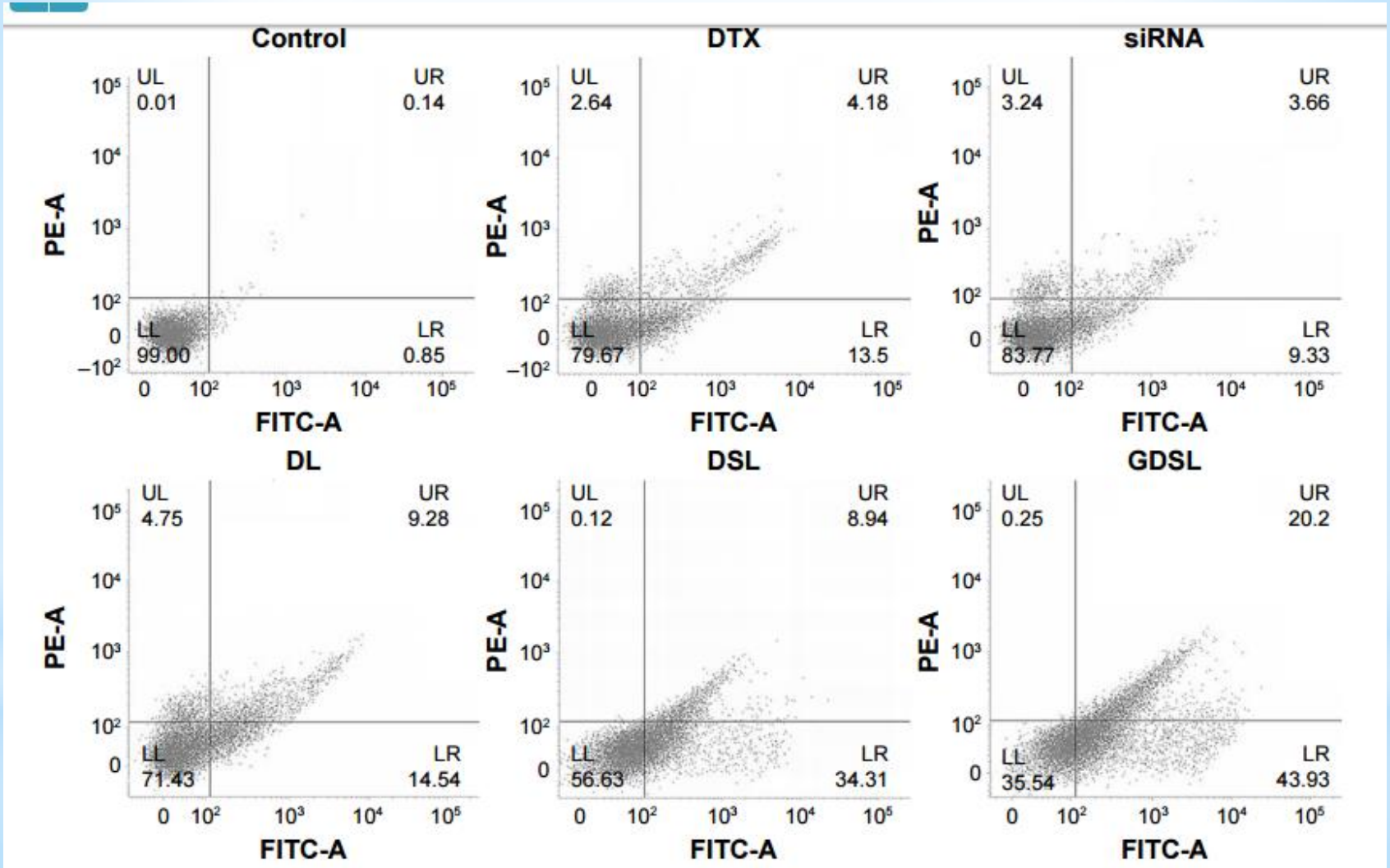


Figure 6 Annexin-V/PI-based apoptosis assays of Hep-2 cells.

Notes: Cells were treated with free DTX, ABCG2–siRNA, DL, DSL, or GDSL constructs. The apoptosis rates were evaluated using flow cytometric analyses.

Abbreviations: DL, DTX-loaded liposome; DTX, docetaxel; DSL, DTX and siRNA-loaded liposome; FITC, fluorescein isothiocyanate; LL, lower left; LR, lower right; PI, propidium iodide; UL, upper left; UR, upper right.

Results and discussion

6- Quantifications of nuclear apoptosis

- Nuclear apoptotic reactions of Hep-2 cancer cells were identified
- using Hoechst 33382 staining techniques.
- The control cell nuclei remained the same size and shape while nuclei treated with the NP formulations became irregular and distorted in shape.

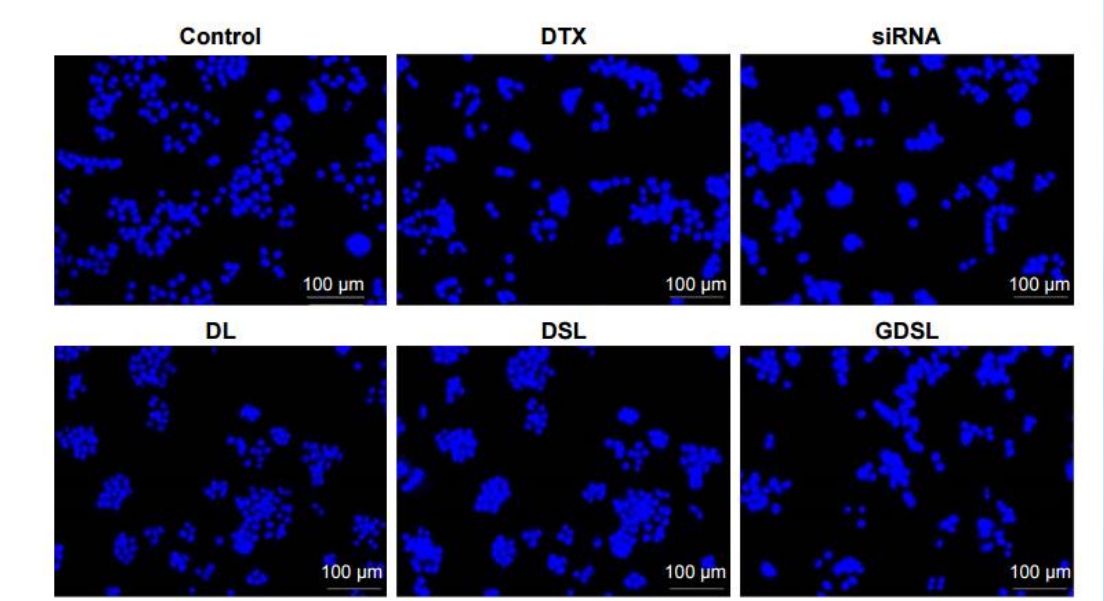


Figure 7 Hoechst 33342-based apoptosis assays of Hep-2 cells.
Notes: Cells were treated with free DTX, ABCG2–siRNA, DL, DSL, or GDSL constructs. Nuclear morphologies of apoptotic cells were visualized using Hoechst staini
Abbreviations: DL, DTX-loaded liposome; DSL, DTX and siRNA-loaded liposome; DTX, docetaxel.

Results and discussion

7- In vivo anti-tumor efficacy assays

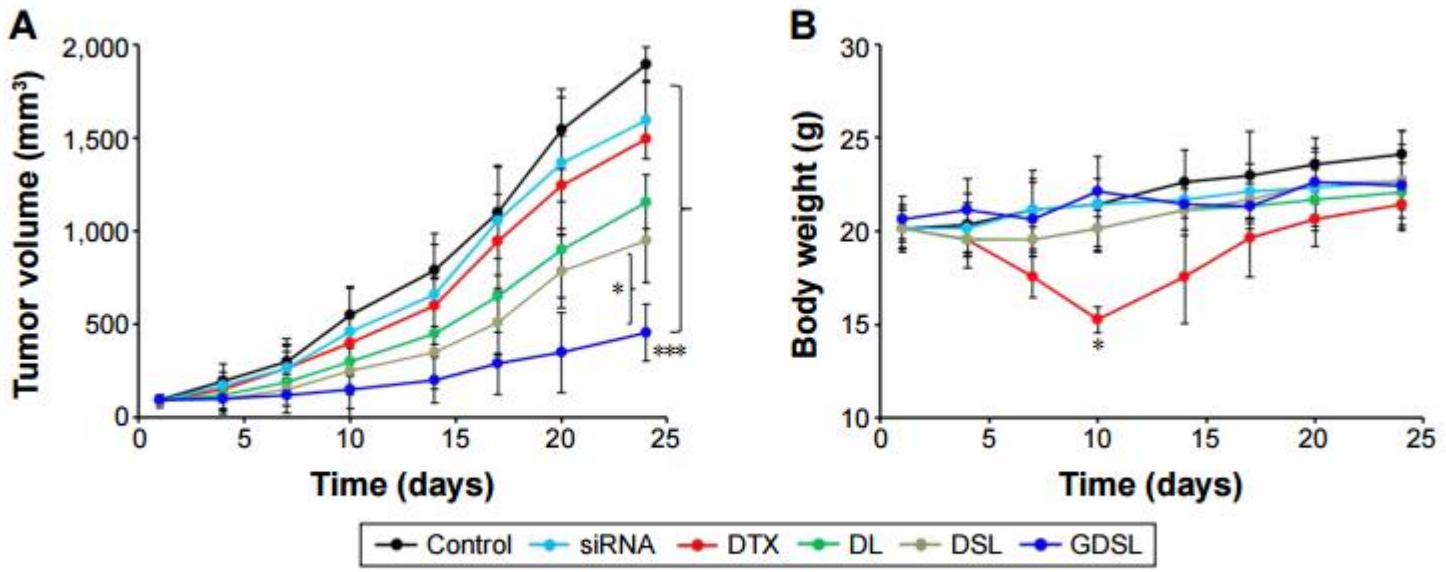


Figure 8 In vivo anti-tumor efficacies of Hep-2 xenograft-implanted murine models.
Notes: Mice bearing Hep-2 tumors were treated with NP formulations, as listed, and (**A**) tumor volumes were measured on days 0–25. (**B**) Body weights were measured to determine toxicity of the treatments. *$P<0.05$; ***$P<0.0001$.
Abbreviations: DL. DTX-loaded liposome: DSL. DTX and siRNA-loaded liposome: DTX. docetaxel: NP. nanoparticle.

Conclusion

1. The data presented here describe dual therapeutic-loaded GE11 peptide-conjugated liposomes that enhanced the combined therapeutic efficacies of DTX and ABCG2– siRNA in laryngeal cancers.

2. GE11 surface peptides enhanced cellular uptake of the constructs in Hep-2 laryngeal cancer cells.

3. Treatment of Hep-2 xenograft-implanted nude mice with the GDSL NP formulation led to smaller tumors than those observed in animals receiving non-targeted NP constructs.

Thank you